

Project Title: Azithromycin for acute COPD exacerbations with hospitalization - the BACE trial

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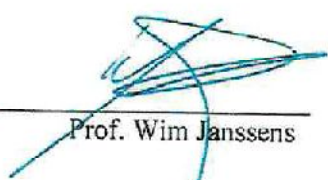
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Contents

1	Purpose.....	5
2	Study Objectives and Endpoints	5
2.1	Study Objective	5
2.2	Study Endpoints.....	5
2.2.1	Primary Efficacy Variable.....	5
2.2.2	Key Secondary Endpoints	5
2.2.3	Other Secondary endpoints	5
3	Study Methods	6
3.1	Overall Study Design and Plan.....	6
3.2	Selection of Study Population	6
3.2.1	Inclusion Criteria.....	6
3.2.2	Exclusion Criteria.....	7
3.3	Method of Treatment Assignment and Randomisation.....	7
3.4	Treatment Masking (Blinding)	7
4	Sequence of Planned Analyses	8
4.1	Interim Analyses.....	8
4.2	Final Analysis and Reporting	8
5	Sample Size Determination.....	8
6	Analysis Sets	8
7	General Issues for Statistical Analysis.....	9
7.1	Analysis Software.....	9
7.2	Summary Statistics	9
7.3	Statistical Comparisons Between Groups	9
7.4	Methods for Withdrawals, Missing Data and Outliers.....	9
7.5	Data Transformations	9
7.6	Multicentre Study	9
7.7	Multiple Comparisons	10
7.8	Planned Subgroups, Interactions and Covariates	10
8	Study Subjects.....	10
8.1	Disposition of Subjects and Withdrawals.....	10
8.2	Protocol Violations and Deviations.....	11
9	Demographics and Other Baseline Characteristics.....	11

10	Efficacy Analyses	11
10.1	Primary Endpoint.....	11
10.2	Key Secondary Endpoints	11
10.2.1	Number of Clinical Failures up to Day 90	12
10.2.2	COPD Assessment Test (CAT) at Day 90	12
10.2.3	Total Days of Additional/Prolonged Systemic Steroid Use at Day 90	12
10.3	Other Secondary Endpoints.....	12
11	Safety Data	14
12	Other Data	14
13	References	14
14	History	14

1 Purpose

This document provides a detailed description of the statistical analyses of the main intervention study that will be performed for the evaluation of the primary, secondary and safety endpoints of the BACE study.

2 Study Objectives and Endpoints

2.1 Study Objective

The large multicenter randomized controlled trial has two main scientific objectives:

1. To prove the effectiveness of azithromycin on top of standard therapy in the acute treatment of COPD exacerbations which require hospitalization.
2. To prove safety without losing effectiveness by reducing dose and duration of a current everlasting treatment.

2.2 Study Endpoints

2.2.1 Primary Efficacy Variable

The primary efficacy variable of interest is time to clinical failure within 90 days. Clinical failure is defined as the composite of death, treatment intensification (additional dose of steroids, switch antibiotics for respiratory reasons or new course of steroids and/or antibiotics) and step up in hospital care for respiratory reasons (from ward to ICU during index event, or from home to ward or ICU (new admission) after discharge).

2.2.2 Key Secondary Endpoints

1. Number of clinical failures up to Day 90
2. COPD Assessment Test (CAT) at Day 90
3. Total days of additional/prolonged systemic steroid use at Day 90

The key secondary endpoints will be tested in hierarchical order in the order above.

2.2.3 Other Secondary endpoints

1. Number of clinical failures up to Day 270.
2. Time to clinical failure up to Day 90 and up to Day 270
3. Time to new exacerbation within 90 and within 270 days. A new exacerbation is defined as the composite of new course of steroids and/or antibiotics, and hospitalization for respiratory reasons, all after the index event.
4. Number of new exacerbations up to 90 days and up to 270 days

5. Total of hospital days within 90 and within 270 days
6. Total days in intensive care within 90 and within 270 days
7. Quality of Life – 5 Dimensions (EQ5D) at Day 90 and Day 270
8. COPD Assessment Test (CAT) at Day 270
9. Modified Medical Research Council (mMRC) at Day 90 and Day 270
10. Speech, Spatial and Qualities of Hearing (SSQ5) questionnaire at Day 90 and Day 270
11. Pre-bronchodilator forced expiratory volume in 1 second (FEV1) at Day 90 and Day 270
12. Total dose of additional/prolonged systemic steroids at Day 270
13. Total days of additional/prolonged systemic steroid use at Day 270.
14. Total days of non-study antibiotics at Day 90 and Day 270
15. Number of home physician contacts at Day 90 and Day 270
16. Average cost of hospitalization at Day 90 and Day 270 including the index hospitalisation
17. Time to death within 90 and within 270 days
18. Time to first treatment intensification within 90 and within 270 days
19. Time to first step up in hospital care for respiratory reasons within 90 and within 270 days.

3 Study Methods

3.1 Overall Study Design and Plan

This study was designed as a double-blind, multicenter, parallel-group, comparative, randomized study.

3.2 Selection of Study Population

All patients will be expected to meet all inclusion and exclusion criteria before entering the study:

3.2.1 Inclusion Criteria

1. Established diagnosis of COPD by medical doctor (based on clinical history OR pulmonary function test).
2. Smoking history of at least 10 pack-years (10 pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.).
3. Current hospitalization for potential infectious AECOPD treated with standard therapy (standard therapy is defined in the study protocol under 2.3 Details study visits and required study assessments, D0 Hospital admission).

4. History of at least one exacerbation during the last year (prior to the current hospital admission) for which systemic steroids and/or antibiotics were taken.
5. ECG at admission.

3.2.2 Exclusion Criteria

1. Mechanical or non-invasive ventilation at moment of randomization (D1).
2. Long QT interval on ECG (QTc > 450msec for males or > 470msec for females).
3. History of life-threatening arrhythmias.
4. Myocardial infarction (NSTEMI or STEMI) less than 6 weeks before start of study drug.
5. Unstable angina pectoris or acute myocardial infarction (NSTEMI or STEMI) at admission.
6. Drugs with high risk for long QT interval and torsade de pointes (amiodarone, flecainide, procainamide, sotalol, droperidol, haldol, citalopram, other macrolides)
7. Documented uncorrected severe hypokalemia ($K^+ < 3.0$ mmol/L) or hypomagnesemia ($Mg^{2+} < 0.5$ mmol/L).
8. Chronic systemic steroids (> 4 mg methylprednisolone /day for ≥ 2 months).
9. Actual use of macrolides for at least 2 weeks.
10. Allergy to macrolides.
11. Active cancer treatment.
12. Life expectancy < 3 months.
13. Pregnant or breast-feeding subjects. Woman of childbearing potential must have a pregnancy test performed and a negative result must be documented before start of treatment.

3.3 Method of Treatment Assignment and Randomisation

Patients will be randomly assigned in a 1:1 ratio to receive either azithromycin or placebo, with a permuted block size of ten and sequential assignment, stratified by center. Randomization and distribution of the study medication is performed by the hospital pharmacy of the University Hospital of Ghent based on an online generated randomization schedule (<http://www.randomization.com>). Unique randomization codes are locally obtained through a secured web-based program.

3.4 Treatment Masking (Blinding)

Participants, investigators and research assistants are masked to treatment allocation.

The identity of study medication will be concealed by the use of a format that is identical in packaging, labelling, schedule of administration and appearance.

At all times, randomization codes are kept strictly confidential during the study, with exception of an ad hoc independent safety committee adjudicating cardiovascular side effects and mortality after 300 patients. Nevertheless, code breaks will be available at the site and un-blinding may occur in the case of an emergency (SAE) which will require knowledge of the treatment assignment.

4 Sequence of Planned Analyses

4.1 Interim Analyses

An interim analysis for efficacy and futility was planned when 300 patients would have reached their 90-day follow-up. However, due to slow recruitment and the unavailability of additional funds to prolong the study, it was decided to stop the study early and perform the final analysis on the 301 randomized patients when all patients have reached their 270-day follow-up.

4.2 Final Analysis and Reporting

Upon final database lock, statistical analyses of the data will be performed according to the methods described in this document.

Any deviations will be documented. The analysis populations and analysis plan will be defined prior to database lock.

5 Sample Size Determination

250 subjects per group, 500 subjects in total, will yield 80% power to show a significant difference in the primary endpoint at a two-sided significance level of 0.05. Sample size calculation is based on a survival analysis using a log-rank test assuming proportional hazards, a clinical failure in at least 45% of the placebo arm within 3 months (based on 35% readmissions in the Belgian COPD population in the European COPD audit (Lopez-Campos et al., 2013), a proportion of 50% with a new exacerbation within 4 months after randomization in the randomized trial with vitamin D enrolling similar but stable patients (Lehouck, et al, 2012), and a 20% treatment failure within 8 weeks in the MAESTRAL study looking at mild exacerbations (Wilson et al, 2012)), a 35% relative improvement with azithromycin intervention (HR = 0.65) (HR 0.73 in NEJM for time to first exacerbation (Albert et al., 2011), HR of 0.5 for time to resolution of ventilator associated pneumonia (Giamarellos-Bourboulis et al; 2008) and taking into account a maximal amount of 25% of drop-outs.

After the inclusion of 125 patients, recruitment was somewhat lower than anticipated and the observed dropout was also lower (16/125 [12.8%]). Therefore, it was opted to foresee an interim analysis for efficacy and futility when 300 patients reach their 90-day follow-up. Assuming a lower dropout rate of 17% and the same other assumptions as mentioned earlier, the trial remains powered at 80% with a sample size of 500 patients and a total number of 177 events.

6 Analysis Sets

All randomized patients will be analysed according to the intention-to-treat principle.

Therefore, the primary analysis set of interest will be the Full Analysis Set (FAS), which will include all randomised patients, according to their randomised treatment.

In addition, the primary endpoint will also be assessed in the Per Protocol Set (PPS), which will consist of all FAS patients, excluding those with major protocol violations. Patients will be analysed according to their actual treatment. Relevant major protocol violations will be defined prior to database lock.

7 General Issues for Statistical Analysis

7.1 Analysis Software

All analyses will be performed using SAS software version 9.4 (1) and R 3.1.3 (2) for Windows or higher.

7.2 Summary Statistics

Continuous variables will be summarized by the number of non-missing data points, mean, standard deviation, median and interquartile range.

Categorical and ordinal variables will be summarized by treatment group by observed frequencies and percentages relative to the total number of non-missing items.

7.3 Statistical Comparisons Between Groups

Continuous variables will be compared using a t-test or Wilcoxon rank-sum test, as appropriate.

Categorical variables will be compared using a chi-squared or Fisher's exact test, as appropriate.

All tests will be two-sided.

For the analysis of the primary and secondary endpoints, estimated treatment effects and associated 95% two-sided confidence intervals will be presented.

7.4 Methods for Withdrawals, Missing Data and Outliers

The primary efficacy variable and most of the secondary endpoints are survival endpoints, and hence, early withdrawals are simply censored at their time of withdrawal.

No imputations of other variables is foreseen.

7.5 Data Transformations

Not applicable

7.6 Multicentre Study

Although randomization was stratified by study site, no account will be taken of study site in the analysis.

7.7 Multiple Comparisons

Multiplicity due to the interest in 3 key secondary endpoints will be addressed by means of a serial gatekeeping procedure.

7.8 Planned Subgroups, Interactions and Covariates

The following subgroups and interactions will be assessed for the primary and key secondary endpoints in the FAS:

- age > 65 or ≤ 65 year
- Male vs female
- Smoker vs ex-smoker (stopped smoking > 6 months)
- GOLD A, B vs GOLD C vs GOLD D
- Former GOLD I, II vs III vs IV
- High CRP (> 50 mg/dL) vs low CRP (< 50 mg/dL)
- Anthonissen I vs Anthonissen II vs Anthonissen III
- ICS use vs no ICS use

Further subgroup/interaction analyses will be decided upon during the blind review meeting prior to database lock.

8 Study Subjects

8.1 Disposition of Subjects and Withdrawals

A patient flow chart as documented in the CONSORT guidelines for the reporting of randomized clinical trials will be provided.

A summary by treatment group will be provided for the following:

- Number of study subjects
- Number of randomized subjects, i.e. included in FAS
- Number of treated subjects
- Number of patients excluded from the PPS due to major protocol violations and type of violations
- Number of patients included in PSS
- Number of patients attending Day 90 assessment
- Number withdrawing prior to Day 90
- Number who died prior to Day 90

- Number lost to follow-up prior to Day 90
- Number of patients attending Day 270 assessment
- Number withdrawing between Day 90 and Day 270
- Number who died between Day 90 and Day 270
- Number lost to follow-up between Day 90 and Day 270

8.2 Protocol Violations and Deviations

Important protocol violations and deviations that can impact the results of the statistical analyses will be fully documented prior to database lock.

9 Demographics and Other Baseline Characteristics

All data recorded at baseline will be summarized by treatment group.

Since this was a double-blind study, no comparisons of baseline characteristics between the treatment groups will be done.

Summaries will be presented for both FAS and PPS.

10 Efficacy Analyses

10.1 Primary Endpoint

Time to clinical failure within 3 months for the 2 groups will be assessed by means of Kaplan-Meier methodology and compared between groups using a log-rank test. Patients who did not have a clinical failure within 90 days will be censored at 90 days.

The effect of treatment will be estimated by a hazard ratio, obtained from a Cox regression including randomized treatment as factor, and presented along with its two-sided 95% confidence interval.

The 5th, 10th and 25th percentiles of time to clinical failure will be estimated for both treatment groups and presented along with their 95% confidence intervals.

10.2 Key Secondary Endpoints

To control the overall Type I Familywise Error Rate (FWER) of the key secondary endpoints, a serial gatekeeping method will be used:

If the analysis of the primary endpoint shows a statistically significant difference between the treatment groups, the key secondary endpoints will be tested in hierarchical order, beginning with the first key secondary endpoint. Testing of each of the following endpoints will only be done if the previous endpoint was found to be statistically significant. The following order will be used:

1. Number of clinical failures up to Day 90
2. COPD Assessment Test (CAT) at Day 90
3. Total days of steroid use at Day 90

10.2.1 Number of Clinical Failures up to Day 90

The number of clinical failures will be assessed by means of the Mean Cumulative Function (MCF), which will be estimated using non-parametric methods by randomised treatment group and presented graphically versus time since the start of the study. Note that only clinical failures up to Day 90 will be included in the analysis.

In addition, a plot will be provided of the difference in MCF between groups versus time.

The two treatment groups will be compared using a log-rank test for MCFs.

The treatment effect will be estimated by the difference in MCF at 90 days and will be presented along with its 95% confidence interval.

10.2.2 COPD Assessment Test (CAT) at Day 90

Total CAT scores will be summarised by treatment and visit.

To account for missing data, the CAT scores will be analysed using a longitudinal model that includes data collected at all visits up to day 270.

The statistical analysis will be done using a weighted GEE (generalized estimating equations) model with identity link and a normal distribution for the residuals. An independent working correlation matrix will be used to account for the repeated nature of the data. The GEE model will include factors for randomised group and visit and the interaction between the two. The baseline value will be included as a covariate in the model. The missing model will include the same factors as the GEE model.

The treatment effect will be estimated by the difference in expected values at Day 90 between the two treatment groups and presented along with its 95% confidence interval.

10.2.3 Total Days of Additional/Prolonged Systemic Steroid Use at Day 90

The total number of days that a patient used additional/prolonged steroids up to Day 90 will be summarised by randomised treatment.

The statistical analysis will be done using a Poisson regression on the number of days of additional/prolonged steroid use, using the natural logarithm of the total number of days in the study up to 90 days (i.e. maximum 90 days) as offset. The model will only include a factor for randomised treatment.

The treatment effect will be estimated by the rate ratio and presented along with its 95% confidence interval.

Over-or underdispersion of the data will be assessed and if found, appropriate alternatives will be used to analyse the data (e.g. zero-inflated Poisson regression, ...).

10.3 Other Secondary Endpoints

All other secondary endpoints will be summarised by randomised treatment and visit, if applicable.

Since all analyses of the other secondary endpoints are of an exploratory nature, no adjustments will be made to the significance level and all endpoints will be assessed at a significance level of 5%.

The following endpoints will be analysed using the same methodology as for the primary endpoint, described in section 10.1:

- Time to clinical failure up to Day 90 and up to Day 270;
- Time to death within 90 and within 270 days
- Time to first treatment intensification within 90 and within 270 days
- Time to first step up in hospital care for respiratory reasons within 90 and within 270 days

The following endpoints will be analysed using the same methodology as described in section 10.2.1:

- Number of clinical failures up to Day 270;

The following endpoints will be analysed using the same methodology as described in section 10.2.2:

- Quality of life – EQ5D at Day 90 and Day 270;
- COPD assessment test (CAT) at Day 270;
- Modified Medical Research Council (mMRC) at Days 90 and 270;
- SSQ5 questionnaire at Day 90 and 270;
- Pre-bronchodilator FEV1 at Days 90 and 270, but not including baseline as a covariate;

The following endpoints will be analysed using the same methodology as described in section 10.2.3:

- Total of hospital days within 90 and 270 days;
- Total days in intensive care within 90 and 270 days;
- Total dose of additional/prolonged systemic steroids at Days 270;
- Total days of additional/prolonged systemic steroid use at Day 270;
- Total days of non-study antibiotics use at Days 90 and 270;
- Number of home-physician contacts at Days 90 and 270.

Time to new exacerbation within 90 and within 270 days will be analysed using the cumulative incidence function (CIF) with all-cause death as a competing risk. For each time point, the event rate with a 95% CI (using a log-log transformation) in each treatment group separately and the between group comparison will be done by Chi-square test and a risk ratio with a 95% CI.

The number of new exacerbation within 90 and within 270 days will be analysed using MCF with all-cause death as a competing risk (Dong et al., 2015). For each time point, the event rate with a 95% CI in each treatment group separately and the between group comparison will be done by a Z-test and the difference in MCF with a 95% CI will be reported.

The average cost of hospitalisation at Days 90 and 270 will be analysed by means of Wilcoxon rank-sum test. In addition to the p-value, the Hodges-Lehman estimator with a 95% confidence interval to quantify the treatment effect will be reported, respectively.

11 Safety Data

The number of patients with AEs (SAEs), serious AEs, treatment-related AEs and fatal will be summarized by randomized treatment group for the FAS.

12 Other Data

All remaining data will be summarized by treatment and visit, if applicable.

13 References

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14 History

1.0 : original version

2.0 : removed interim analysis and all references to it.